

Reply to the Comment on “Passage Times for Unbiased Polymer Translocation through a Narrow Pore”

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The main point raised in the Comment of Huopaniemi *et al.* [1] concerns the scaling of the mean time $\langle\tau_u\rangle$ it takes a polymer of length N , threaded halfway in a narrow pore, to unthread, in the absence of any external field or pulling force on the polymer (i.e., for unbiased translocation). As argued in our paper [5], the mean dwell time $\langle\tau_d\rangle$ that a translocating polymer spends in the pore scales with polymer length N in the same way as the unthreading time. We specifically studied this for polymers in three dimensions, whose dynamics is described by the combination of reptation and Rouse dynamics; i.e., hydrodynamics is neglected.

On the theoretical side, a relevant time scale for this problem is the Rouse time τ_R , which is the longest time scale for a polymer in bulk solution to relax in the absence of external forces. As a function of polymer length N , the Rouse time scales as $\tau_R \sim N^{1+2\nu}$. We verified that this scaling holds in the lattice polymer used in our simulations, and also that the Rouse time is the longest time scale for a polymer tethered to a fixed membrane [6]. Since the mobility of a polymer threaded in a pore will not exceed that of an unrestricted polymer, it follows that $\langle\tau_d\rangle \geq \tau_R$ [2, 5]. In the existing literature, there is *no theoretical argument* for this inequality to reduce to an equality. There is however *numerical* evidence in 2D that this inequality is saturated in Ref. [2], as well as in the Comment and the earlier works of the authors of the Comment. With the number s of the monomer located in the pore taken as a reaction coordinate, a consequence of the above inequality is that the diffusion of this reaction coordinate has to be anomalous, i.e. the mean squared displacement $\langle\Delta s^2(t)\rangle \sim t^\alpha$ with an anomalous dynamics exponent $\alpha \leq 2/(1+2\nu)$. Again, there is no theoretical argument why also this inequality should be saturated.

Since both α and the scaling $\langle\tau_d\rangle \sim \tau_R$ in Ref. [2] were obtained solely from *a single set of simulations to calculate* $\langle\tau_d\rangle$, our first remark concerns the *factual misrepresentations* by the Comment’s authors, to suggest that the results of Ref. [2] are “well-established”. The authors of the comment wished to settle these with simulations alone.

There is plenty of numerical evidence that points towards different scaling of $\langle\tau_d\rangle$ than τ_R , both in 3D and in 2D. In our paper we reported a numerical exponent 2.40 ± 0.05 for unbiased translocation in 3D [5]. Another group, using a completely different polymer model, reported an exponent 2.52 ± 0.04 [7]. In subsequent works,

we have provided a *full theoretical description* of this problem, leading to the result $\langle\tau_d\rangle \sim N^{2+\nu}$ both in 3D [6, 8] and in 2D [9]. This theoretical description is supported by high-precision numerical simulations, for which the 3D results we provide below in Table I.

N	τ_u	$\tau_u/N^{2+\nu}$
100	65136	0.434
150	183423	0.428
200	393245	0.436
250	714619	0.445
300	1133948	0.440
400	2369379	0.437
500	4160669	0.431

Table I: Median unthreading time over 1,024 runs for each value of the polymer length N in 3D. Data taken from Ref. [8].

The only numerical evidence contradicting our theory, as far as we are aware of, is the newly produced numerical result in the Comment, and that of Wei *et al.* [10]. However, it is unclear whether the simulations using GROMACS by the Comment’s authors or those used by Wei *et al.* implement purely Rouse and reptation dynamics, as is the assumption in all theoretical work mentioned here. Moreover, the authors [1, 10] have taken N only up to 200, from which an attempt to recover scaling results for $\langle\tau_d\rangle$, in our opinion, is misleading. Specially, since one is dealing with a numerical difference of order 10%, the discrepancy between different simulation results can easily be due to finite- N effects; replacing N by $N + \sqrt{N}$ or $N - \sqrt{N}$ produces double-logarithmic plots in which the data can be fitted about equally well by straight lines, however with exponents that deviate easily 10% or more. We do not believe that this apparent discrepancy can be resolved by simulations alone.

Although the full derivation of the result $\langle\tau_d\rangle \sim N^{2+\nu}$ can be found elsewhere [6, 8, 9], for the sake of completeness we summarize it below.

Translocation takes place via the exchange of monomers through the pore. This exchange responds to $\phi(t)$, the difference in chain tension perpendicular to the membrane; simultaneously, $\phi(t)$ adjusts to $v(t) = \dot{s}(t)$, the transport velocity of monomers across the pore, as well! With $\Delta s(t)$ as the total number of monomers translocated from one side to the other in the time interval $[0, t]$,

and $\phi(t)$ playing the role of chemical potential difference across the pore, the two variables $\Delta s(t)$ and $\phi(t)$ are conjugate to each other in the thermodynamic sense. In the presence of memory effects, they are related to each other by $\phi(t) = \int_0^t dt' \mu(t-t')v(t')$ via the memory kernel $\mu(t)$, which can be thought of as the (time-dependent) ‘impedance’ of the system. This relation can be inverted to obtain $v(t) = \int_0^t dt' a(t-t')\phi(t')$, where $a(t)$ can be thought of as the ‘admittance’. In other words, in the Laplace transform language, $\mu(k) = a^{-1}(k)$, where k is the Laplace variable representing inverse time. Additionally, via the fluctuation-dissipation theorem, they are related to the respective autocorrelation functions as $\mu(t-t') = \langle \phi(t)\phi(t') \rangle_{v=0}$ and $a(t-t') = \langle v(t)v(t') \rangle_{\phi=0}$.

In Ref. [8] we showed that $\mu(t) \sim t^{-\frac{1+\nu}{1+2\nu}} \exp(-t/\tau_R)$ in 3D. This implies that the translocation dynamics is anomalous for $t < \tau_R$, i.e., $\langle \Delta s^2(t) \rangle = \int_0^t dt' (t-t')a(t')$, the mean-square displacement of the monomers through the pore, behaves as t^{α_1} for some $\alpha_1 < 1$. Beyond the Rouse time the translocation dynamics becomes simply diffusive. From the behaviour of $\mu(t)$ above, it is easily shown that $\alpha_1 = \frac{1+\nu}{1+2\nu}$: having ignored the $\exp(-t/\tau_R)$ term for $t < \tau_R$, one obtains $\mu(k) \sim k^{-\frac{\nu}{1+2\nu}}$, implying $a(k) \sim k^{\frac{\nu}{1+2\nu}}$, i.e., $a(t) \sim t^{-\frac{1+3\nu}{1+2\nu}}$, which yields $\alpha_1 = \frac{1+\nu}{1+2\nu}$.

Thus, for $t < \tau_R$, $\langle \Delta s^2(t) \rangle \sim t^{\frac{1+\nu}{1+2\nu}}$ and for $t \geq \tau_R$

$\langle \Delta s^2(t) \rangle \sim t$, which together yield $\langle \tau_d \rangle \sim N^{2+\nu}$, both in 3D and 2D. Moreover, using high-precision simulation data, we demonstrated that in 2D the probability distribution of the dwell time $P(\tau_d)$, behaves as $P(\tau_d) \sim \mathcal{P}(\tau_d/N^{2+\nu})/N^{2+\nu}$, with a scaling function $\mathcal{P}(t)$ [9].

To conclude, to date no theoretical argument has been reported for why $\langle \tau_d \rangle$ should scale as τ_R . In fact there is a derivation why the scaling with polymer length N for the two should differ [6, 8, 9]. Numerical evidence [6, 7, 8, 9] also points towards a scaling of $\langle \tau_d \rangle$ different from τ_R , apart from those due to the Comment’s authors and that due to Wei et al. [10]. The theoretical formalism that yields $\langle \tau_d \rangle \sim N^{2+\nu}$ for unbiased translocation also works beautifully for translocation mediated by a pulling force at the head of the polymer [11], and field-driven translocation [9, 12], providing a *solid unified theoretical understanding of the dynamics of translocation*, based on the well-known laws of polymer physics.

We end our reply with the additional observation that the expression for $\langle \tau_d \rangle$ for pore length L provided in the Comment [1, 3], too, is incorrect. There is general agreement that the monomers inside the pore show anomalous diffusion with some exponent $\alpha \leq 2/(1+2\nu)$, as discussed above. With this kind of dynamics, the time to travel over a distance L has to increase faster than quadratically.

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